Attorney Docket No.: 26230

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

DIETRICH, et al.

Serial No.: 10/505,138 Group Art: 1618

Filed: August 19, 2004 Examiner: SILVERMAN, E.

For: **ORAL DOSAGE FORM CONTAINING A PDE 4 INHIBITOR AS AN ACTIVE INGREDIENT AND POLYVINYLPYRROLIDON AS EXCIPIENT**

TRANSMITTAL LETTER

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Submitted herewith for filing in the U.S. Patent and Trademark Office is the following:

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Respectfully submitted,
The Nath Law Group, PLLC

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MAIL STOP APPEAL BRIEF-PATENTS
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DIETRICH, et al. Confirmation No. 1681

Serial No.: 10/505,138 Group Art Unit: 1618

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For: **ORAL DOSAGE FORM CONTAINING A PDE 4 INHIBITOR AS AN ACTIVE INGREDIENT AND POLYVINYLPYRROLIDON AS EXCIPIENT**

APPEAL BRIEF

This is an appeal to the Board of Patent Appeals and Interferences from the decision of Examiner Eric Silverman, mailed November 12, 2008, rejecting claims 38-39, 41-48, 53-54, 65, 68-79, and 81-87. Appellants filed a Notice of Appeal on January 30, 2009, making this Appeal Brief due by March 30, 2009. Accordingly, this paper is timely filed.

1. **Table of Contents**

2. The Real Party in Interest

The real party in interest in this appeal is NYCOMED GmbH.

3. Related Appeals and Interferences

Appellants are not aware of any other appeals or interferences that will directly affect, or be directly affected by, or have a bearing on the Board's decision in this appeal.

4. **Status of Claims**

The status of the claims is as follows upon filing of this Appeal Brief:

Claims cancelled: 1-37, 40, 49-52, 55-64, 66-67, and 80

Claims withdrawn from consideration but not cancelled: None

Claims pending: 38-39, 41-48, 53-54, 65, 68-79, and 81-87

Claims objected to: None

Claims allowed: None

Claims rejected: 38-39, 41-48, 53-54, 65, 68-79, and 81-87

The claims on appeal are 38-39, 41-48, 53-54, 65, 68-79, and 81-87.

5. Status of Amendments

Appellants filed a Preliminary Amendment on August 19, 2004, in which claim 1 was canceled, claims 2-3 and 6-10 were amended, and claims 12-17 were added.

Appellants filed an Amendment and Response on December 1, 2005, in which claims 1-17 were canceled, and claims 18-65 were added.

Appellants filed an Amendment and Response on June 1, 2006, in which claims 24-25 were amended.

Appellants filed a Supplemental Amendment on August 1, 2006, in which claim 24 was canceled, claim 18 was amended, and claims 66-67 were added.

Appellants filed an Amendment and Response on April 27, 2007, in which claims 33-35 and 67 were amended.

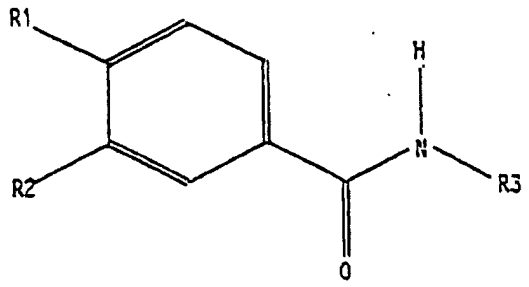
Appellants filed an Amendment and Response on August 29, 2007, in which claims 18-23, 25-37, 49-52, 56-64, and 66-67 were canceled, claims 38, 42-43, 47, and 53 were amended, and claims 68-87 were added.

Appellants filed an Amendment and Response on July 25, 2008, in which claims 40, 55, and 80 were canceled, and claims 38, 47, 53, 68, and 81-84 were amended. The Examiner subsequently issued an Official Action dated November 12, 2008, in which the amendments were entered but the rejection of all claims was maintained. As such, Appellants submit that claims 38-39, 41-48, 53-54, 65, 68-79, and 81-87 are the currently pending claims of record. The claims listed in the claims appendix herein incorporate the claim amendments of the aforementioned Amendment and Response.

6. Summary of Claimed Subject Matter

The present claims relate to a novel, unobvious process for producing an immediate release dosage form for oral administration of a PDE 4 inhibitor of formula I and comprising polyvinylpyrrolidone.

Pending independent claim 38 claims a process for producing a dosage form for oral administration of a PDE 4 inhibitor, comprising the steps: (a) producing a mixture of a PDE 4 inhibitor of formula I and one or more pharmaceutical excipients

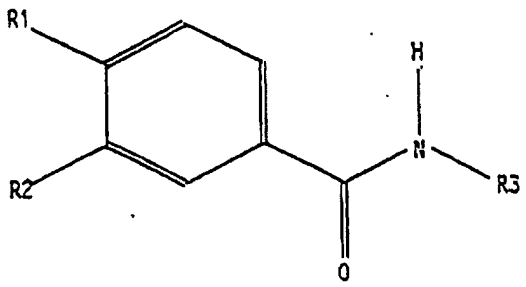


(I)

in which R1 is difluoromethoxy, R2 is cyclopropylmethoxy and R3 is 3,5-dichloropyrid-4-yl,

or a salt of this compound, an N-oxide of the pyridine of this compound or a salt thereof; and (b) granulating the mixture obtained in (a) with an aqueous solution of polyvinylpyrrolidone; wherein the dosage form is in tablet form, wherein said dosage form has immediate release of the PDE 4 inhibitor. Basis for this claim is found, for example, on page 3, line 16, to page 4, line 3; page 4, lines 14-15; page 5, lines 14-16; page 6, lines 8-10; and page 8, lines 3-16.

Pending independent claim 47 claims a process for producing a dosage form for oral administration of a PDE 4 inhibitor, comprising the steps: (a) producing a mixture of pharmaceutical excipients; and (b) granulating the mixture obtained in (a) with a suspension of a PDE 4 inhibitor of formula I in an aqueous solution of PVP

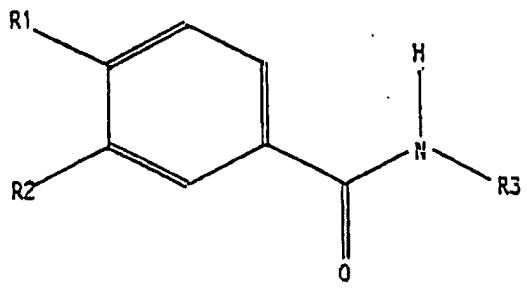


(I)

in which R1 is difluoromethoxy, R2 is cyclopropylmethoxy and R3 is 3,5-dichloropyrid-4-yl,

or a salt of this compound, an N-oxide of the pyridine of this compound or a salt thereof; wherein the dosage form is in tablet form, wherein said dosage form has immediate release of the PDE 4 inhibitor. Basis for this claim is found, for example, on page 3, line 16, to page 4, line 3; page 4, lines 14-15; page 5, lines 14-16; page 6, lines 8-10; and page 8, lines 3-16.

Pending independent claim 53 claims a process for producing a dosage form for oral administration of a PDE 4 inhibitor, comprising the steps: (a) producing an active ingredient preparation in the form of a solid solution in polyvinylpyrrolidone of a PDE 4 inhibitor of formula I,



(I)

in which R1 is difluoromethoxy, R2 is cyclopropylmethoxy and R3 is 3,5-dichloropyrid-4-yl,

or a salt of this compound, an N-oxide of the pyridine of this compound or a salt thereof; (b) producing a mixture of an active ingredient preparation and pharmaceutical excipients and (c) granulating the mixture obtained in (b) with an aqueous solution of polyvinylpyrrolidone; wherein the dosage form is in tablet form, wherein said dosage form has immediate release of the PDE 4 inhibitor. Basis for this claim is found, for example, on page 3, line 16, to page 4, line 3; page 4, lines 14-15; page 5, lines 14-16; page 6, lines 8-10; and page 8, lines 3-16.

7. Grounds of Rejection to be Reviewed on Appeal

A. Rejection of claims 68 and 82-84 under 35 U.S.C. § 112, first paragraph

Whether the identified claims are unpatentable under 35 U.S.C. § 112, first paragraph, as complying with the written description requirement. The Examiner asserts that the phrase "weight average molecular weight" of polyvinylpyrrolidone is allegedly not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the pending claims. The Examiner asserts that since this phrase is allegedly not recited in the specification, and there is no discussion of what type of molecular weight is referred to in the specification, then adding this phrase constitutes new matter.

B. Rejection of claims 38-39, 41, 45-48, 65, 69, 71-79, 81 and 87 under 35 U.S.C. § 103(a)

Whether the identified claims are unpatentable under 35 U.S.C. § 103(a) as obvious over US Published Application No. 20030018071, to Rennard, et al. ("Rennard") in combination with US Patent No. 6,667,362 to Ghebre-Sellassie et al. ("Ghebre-Sellassie") and Remington: The Science and Practice of Pharmacy, 1995 ("Remington").

The Examiner asserts that the primary Rennard et al. reference teaches the combination of certain PDE4 inhibitors with a pharmaceutical carrier. The Examiner admits that Rennard reference does not teach a process for producing a dosage form using PVP in any amount. The secondary Ghebre-Sellassie reference is applied by the Examiner for teaching a method for preparing a drug-PVP dosage forms. See Example I, and claim 1. The Examiner asserts that the Remington reference discusses the use of PVP as a binder for preparation of dosage forms by

using either aqueous or alcoholic solutions. Page 1618, bottom of column 1. The Remington reference also generally discusses methods of producing dosage forms, including a "new method for granulating" called fluid-bed granulation. Page 1625, top of column 2.

The Examiner asserts that it would have been prima facie obvious to a person of ordinary skill in the art to use PVP in conjunction with the disclosure of Rennard, to granulate the PVP in a fluid bed granulator before mixing with an additional excipient, such as magnesium stearate, and tabletting the product. PVP is allegedly obvious to use because Ghebre-Selassie teaches advantages of using PVP, such as increasing bioavailability of poorly soluble drugs. Accordingly, the Examiner concludes it would have been obvious to use a wet granulation process because this is a typical process for formulating PVP containing articles, and because of the advantages described for fluidized bed granulation. The Examiner asserts that because these manipulations are described or suggested by the art, the artisan would enjoy a reasonable expectation of success.

C. Rejection of claims 68 and 82-84 under 35 U.S.C. § 103(a)

Whether the identified claims are unpatentable under 35 U.S.C. § 103(a) as obvious over US Published Application No. 20030018071, to Rennard, et al. ("Rennard") in combination with US Patent No. 6,667,362 to Ghebre-Sellassie et al. ("Ghebre-Sellassie"), Remington: The Science and Practice of Pharmacy, 1995 ("Remington"), as applied to claims 38-39, 41, 45-48, 65, 69, 71-79, 81 and 87 as described above, and further in view of US Patent No. 5,262,711, to Login et al ("Login").

In addition to Rennard, Ghebre-Sellassie, and Remington, the Examiner relies on Login for its alleged teaching of specific molecular weights of PVP for use in tablets. Notably, the

Examiner previously stated on the record that "Login teaches that PVP suitable for use in tablets has is graded as K-30 to K-120 molecular weight. The artisan understands that this corresponds to molecular weights of approximately 9,700 Daltons to 3,470,000 Daltons (see PVP product disclosure, cited on PTO 892)." Page 7 of the Official Action dated February 27, 2008.

The Examiner asserts that it would have been prima facie obvious to a person of ordinary skill in the art to find the optimal molecular weight of PVP within the range taught by Login. Further, the Examiner alleges that the art shows that use of PVP within the useful range will give a predictable result; finding the optimal or working molecular weight of PVP will increase the bioavailability of the drug.

D. Rejection of claims 42-44, 53-54, and 85-86 under 35 U.S.C. § 103(a)

Whether the identified claims are unpatentable under 35 U.S.C. § 103(a) as obvious over US Published Application No. 20030018071, to Rennard, et al. ("Rennard") in combination with US Patent No. 6,667,362 to Ghebre-Sellassie et al. ("Ghebre-Sellassie"), Remington: The Science and Practice of Pharmacy, 1995 ("Remington"), as applied to claims 38-39, 41, 45-48, 65, 69, 71-79, 81 and 87 as described above, and further in view of Chiou et al., "Pharmaceutical Applications of Solid Dispersion Systems", J. Pharm Sci. 60:1281-1302 (1971) ("Chiou"). In addition to Rennard, Ghebre-Sellassie, and Remington, the Examiner relies on Chiou for its alleged teaching the use of solid dispersions of drug with PVP to increase the availability of poorly water soluble drug (1281 – 1283).

The Examiner notes that the "Applicants continue by pointing to the Chiou teaching and allege that it teaches away from the instant claims because it teaches that PVP dispersions should be prepared by a solvent method, and that PVP is soluble in a variety of organic solvents." The

Examiner asserts that the Appellants have failed to recognize that PVP is also well known to be a water soluble. As such, the Examiner asserts that "the artisan looking to Chiou's suggestion of using a solvent in which PVP is soluble, and knowing that PVP is soluble in water, would clearly find it obvious to use water as the granulating liquid." Accordingly, the Examiner asserts that it would have been prima facie obvious to a person of ordinary skill in the art to use a solid dispersion of the drug and PVP, as suggested by Chiou. For these reasons the Examiner concludes that the artisan would enjoy a reasonable expectation of success because Chiou teaches how to make these types of compositions.

E. Rejection of claim 68, 70, and 82-84 under 35 U.S.C. § 103(a)

Whether the identified claims are unpatentable under 35 U.S.C. § 103(a) as obvious over US Published Application No. 20030018071, to Rennard, et al. ("Rennard") in combination with US Patent No. 6,667,362 to Ghebre-Sellassie et al. ("Ghebre-Sellassie"), Remington: The Science and Practice of Pharmacy, 1995 ("Remington"), as applied to claims 38-39, 41, 45-48, 65, 69, 71-79, 81 and 87 as described above, and further in view of Hatzelmann, et al., "Anti-inflammatory and Immunomodulatory Potential of the Novel PDE4 Inhibitor Roflumilast in Vitro", J. Pharm. Exp. Ther., 297:267-279, (2000) ("Hatzelmann").

The Examiner relies on Hatzelmann for its alleged teaching of an N-oxide of the pyridine of the compound (corresponding to the N-oxide of roflumilast), and that both are useful as pharmaceutical agents and as PDE 4 inhibitors (abstract, materials and methods sections).

The Examiner asserts that it would have been prima facie obvious to a person of ordinary skill in the art to use Hatzelmann's N-oxide of roflumilast in the pharmaceutical dosage form suggested by the combination of cited refernece. Obviousness allegedly stems from both

roflumilast and its N-oxide being recognized as pharmaceuticals useful for the same purpose. As such, the artisan would allegedly enjoy a reasonable expectation of success.

8. Argument

A. Rejection of claims 68 and 82-84 under 35 U.S.C. § 112, first paragraph

Appellants respectfully submit that the rejection of the identified claims under 35 U.S.C. § 112, first paragraph, for inadequate written description is improper and should be reversed.

Appellants respectfully submit that the phrase "weight average molecular weight" of polyvinylpyrrolidone would be understood to be described in the specification in such a way as to reasonably convey to one skilled in the art reading the specification that the inventor(s), at the time the application was filed, had possession of the pending claims. One skilled in the art reading the specification would understand the meaning of the phrase "weight average molecular weight" of polyvinylpyrrolidone, and would understand that meaning to be adequately disclosed for at least the following reasons. One of ordinary skill in the art would understand from the various manufacturers' information, and Appellants' specification at page 7, first full paragraph, regarding Kollidon 90 (K90) that this polyvinylpyrollidone has the weight average molecular weight recited in the claims. Further, one skilled in the art would understand that the terms "Kollidon 90" and "K90", for example, have an art-recognized meaning regarding the weight average molecular weight of that particular species of PVP. These are standard art-recognized phrases used to describe a specific weight average molecular weight of the PVP.

Furthermore, in the Examiner's obviousness rejection under 35 USC 103(a) at page 7 of the Official Action dated February 27, 2008, (cited above in section 7(C)) the Examiner describes the cited Login et al. reference as follows (emphasis added):

> **Login teaches that PVP suitable for use in tablets has is graded as K-30 to K-120 molecular weight. The artisan understands that this corresponds to**

molecular weights of approximately 9,700 Daltons to 3,470,000 Daltons (see PVP product disclosure, cited on PTO 892).

Clearly, the Examiner also previously recognized on the record that the artisan understands that the publicly disclosed K-30 to K-120 nomenclature are art-recognized designations corresponding to specific weight average molecular weights of PVP.

For at least the above-discussed reasons, Appellants respectfully submit that the phrase "weight average molecular weight" of polyvinylpyrrolidone would be understood to be described in the specification in such a way as to reasonably convey to one skilled in the art reading the specification that the inventor(s), at the time the application was filed, had possession of the pending claims. Accordingly, Appellants respectfully request that this rejection be withdrawn.

B. Rejection of claims 38-39, 41, 45-48, 65, 69, 71-79, 81 and 87 under 35 U.S.C. § 103(a)

Appellants respectfully submit that the rejection of the identified claims under 35 U.S.C. § 103(a) over Rennard in combination with Ghebre-Sellassie and Remington is improper and should be reversed.

Appellants respectfully submit that Rennard in combination with Ghebre-Sellassie and Remington does not render Appellants' pending claims obvious for at least the following reasons.

To establish a prima facie case of obviousness, three requirements must be satisfied. First, as the U.S. Supreme Court recently held in *KSR International Co. v. Teleflex Inc. et al.*, 550 U.S. 398 (2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a

court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." (*KSR,* supra, slip opinion at 13-15). Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.,* 18 USPQ 1016, 1023 (C.C.P.A 1970). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970). In the present case, the Examiner has failed to make a prima facie case of obviousness because at least one of these three criteria have not been met, if not all.

The Combination of References Do Not Teach or Suggest All Claim Limitations

The primary Rennard et al. reference teaches the combination of certain PDE4 inhibitors with a pharmaceutical carrier. The Rennard reference does not teach each and every element of the presently pending claims. In particular, **Rennard does not teach a process for producing a dosage form using PVP in any amount.**

The secondary Ghebre-Sellassie, et al. reference teaches a method for preparing a drug-PVP dosage form using only "solvent-free" PVP. See Example I, and claim 1. The Ghebre-Selassie method teaches spraying the required plasticizer/solubilizer on a solvent-free complex of PVP and active drug to form granules having a drug-PVP core that is coated with plasticizer/solubilizer. See Example I, and claim 1. Appellants point out that the current process claims recite the use of granulating with an aqueous solution of PVP while the **Ghebre-Selassie method teaches use of only "solvent-free" PVP in the core of the granules**. The Ghebre-Selassie method does not teach adding PVP to the plasticizer/solubilizer spraying solution. Furthermore, the current claims involve granulating with an aqueous solution of PVP to form a PVP-containing dosage form of a water-low-soluble drug, while the Ghebre-Selassie method teaches spraying the required plasticizer/solubilizer on a solvent-free complex of PVP and active drug to form granules having a drug-PVP core coated with plasticizer/solubilizer. **Ghebre-Selassie neither recognizes the need for nor discloses a process for granulating a water-insoluble drug containing mixture with an aqueous solution of PVP to form a PVP-containing dosage form.**

The Remington reference discusses the use of PVP as a binder for preparation of dosage forms by using either aqueous or alcoholic solutions. Page 1618, bottom of column 1. The Remington reference also generally discusses methods of producing dosage forms, including a "new method for granulating" called fluid-bed granulation. Page 1625, top of column 2. However, **the Remington reference neither recognizes the need for nor discloses a process for producing a dosage form wherein an aqueous solution of PVP is used in the granulation step of the production of a dosage form of a low solubility drug as presently claimed.**

Moreover, the combination of references does not correct these deficiencies, and fails to teach a process for producing a dosage form comprising granulating with an aqueous solution of PVP to form a PVP-containing dosage form of a water-low-soluble drug. Rennard does not teach a process for producing a dosage form using PVP in any amount. Ghebre-Selassie teaches spraying their required plasticizer/solubilizer onto a solvent-free complex of PVP and active drug to form granules having a drug-PVP core coated with plasticizer/solubilizer. The Remington reference discusses the use of PVP as a binder for preparation of dosage forms by using either aqueous or alcoholic solutions, and neither recognizes the need for nor discloses a process for producing a dosage form wherein PVP is used in a granulation step for preparing a dosage form of a water-low solubility drug as presently claimed. Combining these teachings does not teach or suggest a process for granulating with an aqueous solution of PVP to form a PVP-containing dosage form of a water-low-soluble drug, as presently claimed

Accordingly, the combination of references cited by the Examiner does not teach or suggest each and every element of the presently pending claims.

There is No Motivation to Combine or Modify the References As Proposed

Appellants submit that even if the cited references teach or suggest all of the recited claim limitations, the combination would not have rendered the rejected claims obvious to one of ordinary skill in the art. Appellants respectfully submit that there is no motivation in the cited references or within the knowledge in the art to combine or modify the references as suggested by the Examiner. For example, the Remington reference neither recognizes the need for nor discloses a process for producing a dosage form by granulating with an aqueous solution of PVP

to form a dosage form of a water-low solubility drug as presently claimed. Thus, a person of ordinary skill would not be motivated, upon reading the Remington's reference, to combine it with the teachings of the other references to obtain a process for producing a dosage form of a slightly soluble drug comprising granulating with an aqueous solution of PVP.

Also, Ghebre-Selassie seeks to produce a solvent-free PVP-drug core coated in a plasticizer/solubilizer solution. There is no suggestion or motivation to modify Ghebre-Selassie by replacing the plasticizer/solubilizer solution with an aqueous PVP solution.

In addition, Appellants submit that **modifying the Ghebre-Selassie method of spraying plasticizer/solubilizer on a solvent-free PVP core to a method of granulating with an aqueous PVP would result in an entirely different composition than that made by the disclosed Ghebre-Selassie method**. Ghebre-Selassie requires the plasticizer/solubilizer spray composition, such as one comprising polyethylene glycol, to obtain the intended PVP-drug core composition. If one were to instead use an aqueous PVP solution, this would absolutely and completely not result in Ghebre-Selassie's intended composition having a drug-PVP core coated with plasticizer/solubilizer. Rather, an entirely new composition would be formed, one which would no longer be the Ghebre-Selassie composition. Only in Appellants' specification can motivation be found for replacing Ghebre-Selassie's plasticizer/solubilizer, such as polyethylene glycol, with an aqueous PVP solution, as asserted by the Examiner. Motivation to modify a combination of teachings can only come from the combination of the cited prior art and the knowledge of one of ordinary skill in the art. Ghebre-Selassie's teachings indicate that such motivation does not exist.

Appellants also note that the present specification, at page 11, first paragraph, indicates that is "has surprisingly been found that dosage forms of the invention produced employing physical mixtures or triturations of the PDE 4 inhibitor whose solubility is slight with a filler...and subsequent granulation with aqueous PVP solutions, or produced employing granulation suspensions of PDE 4 inhibitors in aqueous PVP solutions, have similar advantageous properties in relation to the bioavailability of the PDE 4 inhibitor whose solubility is slight as do dosage forms produced by first producing solid solutions of PVP and PDE 4 inhibitor." This demonstrates that a formulation which contains PVP prepared using the claimed process of making has an unexpectedly favorable dissolution rate of roflumilast.

In fact, other relevant references cited by the Examiner in other rejections indicate that one could not modify the known methods as suggested by the Examiner, and thus there would have been no motivation to combine or modify the references as indicated. For example, Appellants also point out the relevant teachings of Chiou et al., "Pharmaceutical Applications of Solid Dispersion Systems", J. Pharm Sci. 60:1281-1302 (1971) ("Chiou") cited by the Examiner in the obviousness rejection discussed in Section D below. The Chiou reference teaches the use of solid dispersions to increase the availability of poorly water soluble drugs (1281 – 1283). However, while Chiou teaches the use of solid dispersions comprising PVP, **Chiou provides a specific teaching that solid dispersion of drug and PVP can only be prepared by the solvent method**. Chiou teaches at page 1292, 1st column, last paragraph (emphasis added):

> Due to the chemical stability of polyvinylpyrrolidone to heat (81) and its high melting point (probably decomposing before melting at a temperature beyond 250°), **the drug-polyvinylpyrrolidone solid dispersion can only be prepared by the solvent method**.

Appellants submit that this is a direct teaching away from the current claimed process comprising granulating with an aqueous solution of polyvinylpyrrolidone. The Examiner continues to assert that Chiou merely teaches that PVP dispersions **"should be"** prepared by a solvent method. Contrary to the Examiner assertions, Chiou very explicitly states that "**the drug-polyvinylpyrrolidone solid dispersion can only be prepared by the solvent method.**" One of skill in the art reading Chiou in combination with the cited references would understand that **drug-polyvinylpyrrolidone solid dispersions can only be prepared by the solvent method**. The fact that PVP may be soluble in water, as asserted by the Examiner, is not sufficient motivation to overcome Chiou's express teaching that the PVP solid dispersions "**can only be prepared by the solvent method.**"

Furthermore, to support his allegation that the skilled artisan would know of the usefulness of water in preparing solid PVP-drug dispersions, the Examiner at page 4 asserts that

> the artisan looking at Chiou's suggestion of using a solvent in which PVP is soluble, and knowing that PVP is soluble in water, would clearly find it obvious to use water as the granulating liquid.

It appears that the Examiner is asserting that because Chiou teaches that solvents are needed to prepare PVP-insoluble drug solid dispersions, and because PVP is water soluble and water is a solvent, then water is a solvent that can be used to prepare PVP-insoluble solid dispersions. Chiou goes into great deal to describe how PVP is beneficial for releasing drug into an aqueous environment. However, Chiou also clearly suggests three main methods available to prepare solid dispersions: the melting method, the solvent method, and the melting-solvent method. *See* Chiou, p. 1283-1284. Polyethylene glycol is provided as the carrier used in the examples of the melting and melting-solvent methods. PVP is provided as the carrier used in the

examples of the solvent method for preparing a variety of drug-PVP solid dispersions. *See* Chiou, p. 1283, col. 2, second full paragraph. One of the advantages described by Chiou for the solvent method is that "thermal decomposition of drugs or carriers can be prevented because of low temperature required for the evaporation of organic solvents." *See* Chiou, p. 1283, col. 2, third full paragraph. Clearly, water is not an organic solvent and cannot evaporate at the low temperatures at which organic solvents are known to evaporate.

In addition, Chiou, at p. 1283, col. 2, second full paragraph, discloses that the compositions made by the solvent method are "prepared by dissolving a physical mixture of two solid components in a common solvent, followed by evaporation of the solvent", wherein the two solid components are the PVP and the active ingredient. This teaching clearly and specifically requires that both the PVP and the active ingredient are soluble in a common solvent. However, since the present claims require a water-insoluble active ingredient, water cannot be used as a common solvent for both PVP and the presently claimed active ingredient. Accordingly, the skilled artisan reading Chiou would understand that, even though PVP is understood to be water soluble, water is not useful for preparing a PVP-drug solid dispersion for water low soluble substances using the solvent methods known in the art or suggested by the combination of cited references.

No Reasonable Likelihood of Successfully Modifying the References

Further, if the Examiner is suggesting the combination of methods, Appellants submit that the Examiner has no evidence from which it can predict the outcome of such combinations, or have a reasonable expectation of success for the combination. Moreover, there is no

reasonable likelihood of success of modifying the solvent method of Chiou to create an aqueous PVP degranulation method in combination with the cited references. Further, Ghebre-Selassie uses polyethylene glycol, a solubilizer/plasticizer, to successfully attain its PVP-low solubility drug formulation, and which might fit Chiou's description of using polyethylene glycol in a hybrid melting-solvent method. *See* Chiou at the paragraph bridging pages 1283-1284. The combination of Chiou and Ghebre-Selassie clearly do not point to using a granulation step with an aqueous PVP solution to obtain a successful PVP-drug formulation. The combination of references indicates that modifying Ghebre-Selassie by replacing the solubilizer/plasticizer polyethylene glycol with aqueous PVP would not provide a reasonable likelihood of success of obtaining the claimed process.

Moreover, Chiou details many of the various drug-carrier interactions known at that time, including the solvent methods known for preparing PVP-drug solid dispersions, and why solvents are thought to be required for preparing such solid dispersions even though it was known that PVP is soluble in water. One of skill in the art understands that modifying the "solvent method" described in Chiou in view of the teachings of the cited references does not, and cannot, result in the use of an aqueous solution of polyvinylpyrrolidone as recited in the present claims. One of skill in the art would have no reasonable likelihood of success of using water instead of an organic solvent in any known solvent method, or in the methods that are presently claimed where an aqueous solution is used as the granulating solvent, for producing a PVP-low solubility drug solid dispersion because higher temperatures needed to evaporate the water would cause impermissible deterioration of the drug and of the solid composition. The

Examiner must consider all of the relevant art, including the full teachings and suggestions of Chiou, and cannot pick and choose which teachings should be combined.

Accordingly, the combination of art cited by the Examiner does not teach or suggest each and every element of the presently pending claims. Therefore, the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 38-39, 41, 45-48, 65, 69, 71-79, 81 and 87 under 35 USC §103(a).

C. Rejection of claims 68 and 82-84 under 35 U.S.C. § 103(a)

Whether the identified claims are unpatentable under 35 U.S.C. § 103(a) as obvious over US Published Application No. 20030018071, to Rennard, et al. ("Rennard") in combination with US Patent No. 6,667,362 to Ghebre-Sellassie et al. ("Ghebre-Sellassie"), Remington: The Science and Practice of Pharmacy, 1995 ("Remington"), as applied to claims 38-39, 41, 45-48, 65, 69, 71-79, 81 and 87 as described above, and further in view of US Patent No. 5,262,711, to Login et al ("Login"). In addition to Rennard, Ghebre-Sellassie, and Remington, the Examiner relies on Login for its alleged teaching of specific molecular weights of PVP for use in tablets.

In light of the arguments presented in Section B above, Appellants submit that Rennard in combination with Ghebre-Sellassie and Remington does not render Appellants' pending claims obvious. Login cannot remedy these deficiencies present in the combination of Rennard, Ghebre-Sellassie, and Remington. Login, in combination with the cited prior art, provides no further teaching or suggestion to show that drug-polyvinylpyrrolidone dosage forms can be prepared using an aqueous solution of polyvinylpyrrolidone as recited in the present claims. Accordingly, Appellants respectfully request that this rejection be withdrawn.

D. Rejection of claims 42-44, 53-54, and 85-86 under 35 U.S.C. § 103(a)

Whether the identified claims are unpatentable under 35 U.S.C. § 103(a) as obvious over US Published Application No. 20030018071, to Rennard, et al. ("Rennard") in combination with US Patent No. 6,667,362 to Ghebre-Sellassie et al. ("Ghebre-Sellassie"), Remington: The Science and Practice of Pharmacy, 1995 ("Remington"), as applied to claims 38-39, 41, 45-48, 65, 69, 71-79, 81 and 87 as described above, and further in view of Chiou et al., "Pharmaceutical Applications of Solid Dispersion Systems", J. Pharm Sci. 60:1281-1302 (1971) ("Chiou"). In addition to Rennard, Ghebre-Sellassie, and Remington, the Examiner relies on Chiou for its alleged teaching of specific molecular weights of PVP for use in tablets. What is lacking from the teachings of Rennard, '362, and Remington is a teaching of solid solutions. This phrase, as used and defined in the disclosure, is understood to have the same meaning as the phrase "solid dispersion" as used in the Chiou reference. The Chiou reference teaches the use of solid dispersions to increase the availability of poorly water soluble drugs (1281 – 1283).

However, as noted in Section B above, while Chiou teaches the use of solid dispersions comprising PVP, Chiou provides a specific teaching that a solid dispersion of drug and PVP can only be prepared by the solvent method. Chiou teaches at page 1292, 1st column, last paragraph (emphasis added):

> Due to the chemical stability of polyvinylpyrrolidone to heat (81) and its high melting point (probably decomposing before melting at a temperature beyond 250°), **the drug-polyvinylpyrrolidone solid dispersion can only be prepared by the solvent method**.

Appellants submit that this is a direct teaching away from the current claimed process comprising granulating with an aqueous solution of polyvinylpyrrolidone. One of skill in the art reading Chiou in combination with the cited references would understand that **drug-polyvinylpyrrolidone solid dispersions can only be prepared by the solvent method**. Furthermore, one of skill in the art understands that **the "solvent method" described in Chiou does not, and cannot, comprise using an aqueous solution of polyvinylpyrrolidone** as recited in the present claims.

In light of the arguments presented in Section B above, Appellants submit that Rennard in combination with Ghebre-Sellassie and Remington does not render Appellants' pending claims obvious. Chiou cannot remedy these deficiencies present in the combination of Rennard, Ghebre-Sellassie, and Remington. Accordingly, Appellants respectfully request that this rejection be withdrawn.

E. Rejection of claims 68, 70, and 82-84 under 35 U.S.C. § 103(a)

Whether the identified claims are unpatentable under 35 U.S.C. § 103(a) as obvious over US Published Application No. 20030018071, to Rennard, et al. ("Rennard") in combination with US Patent No. 6,667,362 to Ghebre-Sellassie et al. ("Ghebre-Sellassie"), Remington: The Science and Practice of Pharmacy, 1995 ("Remington"), as applied to claims 38-39, 41, 45-48, 65, 69, 71-79, 81 and 87 as described above, and further in view of Hatzelmann et al., Hatzelmann, et al., "Anti-inflammatory and Immunomodulatory Potential of the Novel PDE4 Inhibitor Roflumilast in Vitro", J. Pharm. Exp. Ther., 297:267-279, (2000) ("Hatzelmann").

What is lacking from the teachings of Rennard, Ghebre-Sellassie, and Remington is a teaching of the N-oxide of roflumilast. The Examiner relies on Hatzelmann for its alleged teaching of an N-oxide of the pyridine of the compound (corresponding to the N-oxide of roflumilast), and that both are useful as pharmaceutical agents and as PDE 4 inhibitors (abstract, materials and methods sections).

In light of the arguments presented in Section B above, Appellants submit that Rennard in combination with Ghebre-Sellassie and Remington does not render Appellants' pending claims obvious. Hatzelmann cannot remedy these deficiencies present in the combination of Rennard, Ghebre-Sellassie, and Remington. Hatzelmann, in combination with the cited prior art, provides no further teaching or suggestion to show that drug-polyvinylpyrrolidone dosage forms can be prepared using an aqueous solution of polyvinylpyrrolidone as recited in the present claims. Accordingly, Appellants respectfully request that this rejection be withdrawn.

In view of the foregoing, Appellants respectfully request the reversal of the Examiner's rejections and the allowance of the pending claims. If a fee is required for an extension of time under 37 C.F.R. §1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account No. 14-0112.

Respectfully submitted,

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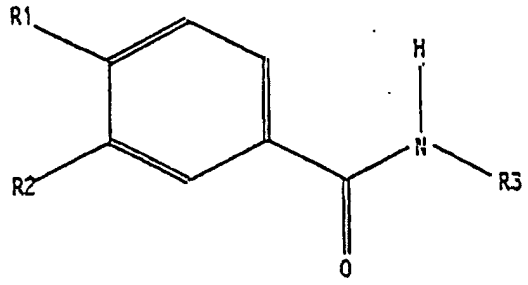
9. Claims Appendix

1.-37. (Canceled)

38. (Previously presented) A process for producing a dosage form for oral administration of a PDE 4 inhibitor, comprising the steps: (a) producing a mixture of a PDE 4 inhibitor of formula I and one or more pharmaceutical excipients



(I)

in which

R1 is difluoromethoxy,

R2 is cyclopropylmethoxy and

R3 is 3,5-dichloropyrid-4-yl,

or a salt of this compound, an N-oxide of the pyridine of this compound or a salt thereof; and

(b) granulating the mixture obtained in (a) with an aqueous solution of polyvinylpyrrolidone;

wherein the dosage form is in tablet or pellet form, wherein said dosage form has immediate release of the PDE 4 inhibitor.

39. (Previously presented) The process according to claim 38, further comprising:

(a) drying the granules,

(b) optionally admixing other pharmaceutical excipients,

(c) mixing with a release agent and

(d) compressing in a tablet press.

40. (Canceled)

41. (Previously presented) The process according to claim 38, wherein the granulating takes place in a fluidized bed granulator.

42. (Previously presented) The process according to claim 38, wherein in step (a) the PDE 4 inhibitor is admixed with the one or more pharmaceutical excipients in the form of a trituration with a pharmaceutical excipient.

43. (Previously presented) The process according to claim 42, which trituration is obtained by grinding the PDE 4 inhibitor with the one or more pharmaceutical excipients.

44. (Previously presented) The process according to claim 42, wherein the pharmaceutical excipient is a filler.

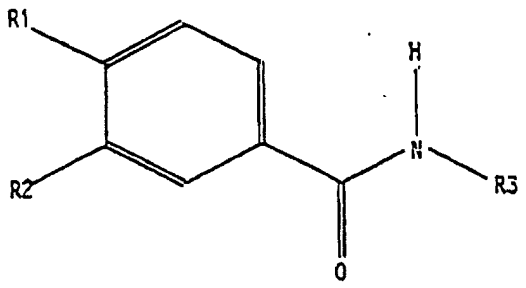
45. (Previously presented) The process according to claim 38, comprising granulating a mixture of (a) a PDE 4 inhibitor of formula I, or a trituration of a PDE 4 of formula I with corn starch, (b) corn starch and (c) lactose monohydrate with an aqueous polyvinylpyrrolidone solution to form granules, drying the granules, mixing the granules with a release agent and compressing the granules in a tablet press.

46. (Previously presented) The process according to claim 38, comprising granulating a mixture of (a) a PDE 4 inhibitor of formula I, or a trituration of a PDE 4 of formula I with corn starch, (b) corn starch, (c) microcrystalline cellulose and (d) sodium carboxymethylstarch with an aqueous polyvinylpyrrolidone solution to form granules, drying the granules, mixing the granules with a release agent and compressing the granules in a tablet press.

47. (Previously presented) A process for producing a dosage form for oral administration of a PDE 4 inhibitor, comprising the steps:

(a) producing a mixture of pharmaceutical excipients; and

(b) granulating the mixture obtained in (a) with a suspension of a PDE 4 inhibitor of formula I in an aqueous solution of PVP



(I)

in which

R1 is difluoromethoxy,

R2 is cyclopropylmethoxy and

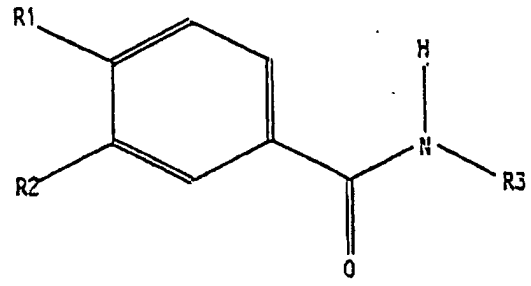
R3 is 3,5-dichloropyrid-4-yl,

or a salt of this compound, an N-oxide of the pyridine of this compound or a salt thereof; wherein the dosage form is in tablet or pellet form, wherein said dosage form has immediate release of the PDE 4 inhibitor.

48. (Previously presented) The process according to claim 47, comprising granulating a mixture of corn starch and lactose monohydrate with a suspension of a PDE 4 inhibitor of formula I in an aqueous solution of PVP to form granules, drying the granules, mixing the granules with a release agent and compressing the granules in a tablet press.

49.-52. (Canceled)

53. (Previously presented) A process for producing a dosage form for oral administration of a PDE 4 inhibitor, comprising the steps: (a) producing an active ingredient preparation in the form of a solid solution in polyvinylpyrrolidone of a PDE 4 inhibitor of formula I,



(I)

in which

R1 is difluoromethoxy,

R2 is cyclopropylmethoxy and

R3 is 3,5-dichloropyrid-4-yl,

or a salt of this compound, an N-oxide of the pyridine of this compound or a salt thereof;

(b) producing a mixture of an active ingredient preparation and pharmaceutical excipients and

(c) granulating the mixture obtained in (b) with an aqueous solution of polyvinylpyrrolidone;

wherein the dosage form is in tablet or pellet form, wherein said dosage form has immediate release of the PDE 4 inhibitor.

54. (Previously presented) The process according to claim 53 for producing a dosage form in the form of a tablet, wherein the granules obtained in step (c) are dried, mixed with lubricants or release agents and compressed in a tablet press.

55.-64. (Canceled)

65. (Previously presented) The process according to claim 43, wherein the pharmaceutical excipient is a filler.

66.-67. (Canceled)

68. (Previously presented) The process according to claim 47, wherein the polyvinylpyrrolidone is selected from the group consisting of polyvinylpyrrolidone of the weight average molecular weight 28,000 – 34,000, polyvinylpyrrolidone of the weight average molecular weight 44,000 – 54,000 and polyvinylpyrrolidone of the weight average molecular weight 1,000,000 – 1,500,000.

69. (Previously presented) The process according to claim 47, wherein the PDE 4 inhibitor is N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxy benzamide (roflumilast).

70. (Previously presented) The process according to claim 47, wherein the PDE 4 inhibitor is the N-oxide of the pyridine of the compound of formula I.

71. (Previously presented) The process according to claim 69, wherein the dosage form contains from 0.01 mg to 5 mg of roflumilast per dosage unit.

72. (Previously presented) The process according to claim 47, wherein the proportion of polyvinylpyrrolidone is from 1 to 5% by weight.

73. (Previously presented) The process according to claim 47, wherein the proportion of polyvinylpyrrolidone is from 2 to 3% by weight.

74. (Previously presented) The process according to claim 47, where the pharmaceutical excipients are excipients selected from the group consisting of fillers, additional binders, tablet disintegrants, lubricants, release agents, flavouring substances, buffer substances, preservatives, coloring substances and emulsifiers.

75. (Previously presented) The process according to claim 47, wherein the proportion of all binders present is from 0.5 to 20% by weight.

76. (Previously presented) The process according to claim 74, which is a tablet and wherein the proportion of filler is from 40 to 99% by weight.

77. (Previously presented) The process according to claim 74, wherein the filler is selected from the group consisting of sugar alcohols, starches, saccharides and mixtures thereof.

78. (Previously presented) The process according to claim 77, wherein the filler is selected from the group consisting of corn starch, microcrystalline cellulose, lactose and mixtures thereof.

79. (Previously presented) The process according to claim 74, wherein the lubricant or release agent is selected from the group consisting of sodium stearyl fumarate, magnesium stearate, calcium stearate, stearic acid, talc and colloidal anhydrous silica.

80. (Canceled)

81. (Previously presented) The process according to claim 47, wherein the pharmaceutical excipients are at least one filler and at least one lubricant or release agent.

82. (Previously presented) The process according to claim 47, comprising

1. Roflumilast 0.125 mg

2. Lactose monohydrate 49.660 mg

3. Corn starch 13.390 mg

4. polyvinylpyrrolidone of the weight average molecular weight 1,000,000 – 1,500,000 1.300 mg

5. Magnesium stearate (vegetable) 0.650 mg.

83. (Previously presented) The process according to claim 47, comprising

1. Roflumilast 0.250 mg

2. Lactose monohydrate 49.660 mg

3. Corn starch 13.390 mg

4. polyvinylpyrrolidone of the weight average molecular weight 1,000,000 – 1,500,000 1.300 mg

5. Magnesium stearate (vegetable) 0.650 mg.

84. (Previously presented) The process according to claim 47 80, comprising

1. Roflumilast 0.500 mg

2. Lactose monohydrate 49.660 mg

3. Corn starch 13.390 mg

4. polyvinylpyrrolidone of the weight average molecular weight 1,000,000 – 1,500,000 1.300 mg

5. Magnesium stearate (vegetable) 0.650 mg.

85. (Previously presented) The process according to claim 47, further comprising producing a solid solution of the PDE 4 inhibitor in the PVP as carrier.

86. (Previously presented) The process according to claim 85, wherein the solid solution is a solid solution with amorphous structure, in which the PDE 4 inhibitor is in the form of a molecular dispersion in the carrier material.

87. (Previously presented) The process according to claim 47, wherein said granulating step (b) is conducted in a fluidized bed granulator.

10. Evidence Appendix

No information is appended under this section.

11. Related Proceedings Appendix

No information is appended under this section.